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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,587	09/06/2001	Antonio Grillo-Lopez	PM0277847	5272

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,587	GRILLO-LOPEZ, ANTONIO	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004 and 26 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08), Paper No(s)/Mail Date 05/24/04; 04/26/04; 04/06/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **04/06/04** has been entered.

Accordingly, claim 1 is being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 103, NEW REJECTION

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maloney DG et al, 1997, Blood, 90(6): 2188-95, in view of Press et al, 1995, Lancet, 346 (8971): 336-340 or Kaminski, MS et al, 1996, J Clin Oncology, 14(7): 1974-81, or US 6,287537 from IDS#OR of 04/06/04, and further in view of Wahl RL et al, May 1998, Proc Annu Meet Am Soc Clin Oncol, 17: 40a, abstract 156, from IDS # ZZZR of o4/06/04.

Claim 1 is drawn to a method for treating a subject having CD20 positive B-cell lymphoma, wherein said subject is refractory to treatment with a non-radiolabeled rituximab antibody, comprising administering to said subject a murine 131-I-labeled anti-CD20 antibody.

It is noted that there is no definition of refractory in the specification, and therefore a subject refractory to treatment with a non-radiolabeled rituximab antibody includes a subject that is resistant to said treatment or that does not show anti-tumor response after administration of a non-radiolabeled rituximab antibody, or a subject that is relapsed after successful treatment with a non-radiolabeled rituximab antibody.

Maloney et al teach treatment of patients with low-grade non-Hodgkin's lymphoma, using Rituximab (IDEC-C2B8), a chimeric monoclonal antibody directed against the B-cell specific antigen CD20 expressed on non-Hodgkin's lymphoma. Maloney et al teach that the response rate is 46% (17 responders from a total of 37 patients).

In other words, 64% of the treated patients are refractory to said treatment.

Maloney et al do not teach treating a subject with CD20 positive B lymphoma that is refractory to treatment with a non-radiolabeled rituximab antibody. Maloney et al do not teach administering to said subject a murine 131-I-labeled anti-CD20 antibody.

Press et al teach treating patients with B-cell lymphomas using I-131 labeled anti-CD20 (B1) antibody, resulting in a progression-free survival of 62% and an overall survival of 93% with a median follow-up of 2 years.

Kaminski, MS et al teach treating B-cell lymphomas with nonmyeloablative doses of anti-CD20 monoclonal antibody labeled with I-131.

US 6,287537 teaches radioimmunotherapy of patients having non-Hodgkin's lymphoma that are reactive with mouse anti-B1 (anti-CD20 antibody), by administering unlabeled anti-B1 antibody followed by I-131 labeled anti-B1 (Examples 1-2 on columns 13-22). US 6,287537 teaches that one factor accounting for the successful results is the targeted radiation effect, besides the antitumor effect of the antibody B1 alone, especially in those cases that the tumors do not response to antibody B1 alone, and a response occurs only after an radiation dose of 131-I labeled B1 (column 21, lines 47-53). US 6,287537 teaches that it is known in the art that low dose-rate irradiation can induce apoptosis in lymphoid cell lines and that antibody binding to cells, including B1 binding, can synergize with this mode of irradiation delivered to targeted tumor cells to induce the anti-tumor therapeutic effects (column 21, third paragraph).

Wahl et al teach that iodine-131 anti-B1 antibody (murine anti-CD20) could be safely readministered to patients with non-Hodgkin's lymphoma that are relapsed.

It would have been prima facia obvious to one of skill in the art to treat CD20 positive B-cell lymphoma patients that are not responsive to non-radiolabeled rituximab antibody, such as those shown in the teaching by Maloney et al, using radiolabeled murine 131-I labeled anti-CD20 antibody, as taught by Press et al, Kaminski, MS et al, or US 6,287537, because radiolabeled murine 131-I labeled anti-CD20 antibody has been successfully used for treating B-lymphoma cells expressing CD20, with a higher progression-free or survival rate than treating with anti-CD20 antibody alone, as shown

when comparing the teaching of Maloney et al with the teaching of Press et al, and because low dose-rate irradiation can induce apoptosis in lymphoid cell lines and further because radiolabeled antibody binding to cells, including B1 binding, can synergize with this mode of irradiation delivered to targeted tumor cells to induce the anti-tumor therapeutic effects, as taught by US 6,287537. One of ordinary skill in the art would have been motivated to treat patients having B-cell lymphoma that are refractory to treatment with the non-radiolabeled chimeric anti-CD20 antibody rituximab, with a reasonable expectation of success, in view of :

1) the successful targeted radiation therapeutic effect of the radiolabeled mouse anti-CD20, as seen, for example, in those cases that tumors do not response to anti-CD20 antibody B1 alone, and a response occurs only after an radiation dose of 131-I labeled B1 as taught by US 6,287537 (column 21, lines 47-53),

2) the synergistic effect of mode of irradiation delivered to targeted tumor cells to induce the anti-tumor therapeutic effects, as taught by US 6,287537, i.e. an enhanced anti-tumor effect due to targeted irradiation by antibody, wherein said targeted irradiation is a different mode of cell killing than that of the chimeric anti-CD20 antibody alone, and

3) the safety of readministration of I-131 labeled anti-B1 antibody (murine anti-CD20) in patients with non-Hodgkin's lymphoma that are relapsed, as taught by Wahl et al; and thus one would have expected that similarly it would be safe to administer I-131 labeled anti-B1 antibody (murine anti-CD20) in patients with B-cell lymphoma that have been previously treated with a non-labeled chimeric anti-CD20 antibody, rituximab.

NO CLAIMS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

August 05, 2004